**DETAILED ACTION**

1. Claims 2-92, 105, 106, 108 and 109 have been cancelled. Claims 95, 98 and 100-104 have been withdrawn. Claims 1, 97, 99, 112, 113, 115 and 121 have been amended.

Claims 1, 93, 94, 96, 97, 99, 107, and 110-121 are under examination.

2. The rejection of Claims 1 and 110-120 under 35 U.S.C. 112, second paragraph, as being indefinite claims 1 and 110-120 under 35 U.S.C. 112, second paragraph, as being indefinite is withdrawn in response to Applicant's amendments to the claims filed on 07/31/2009.

The rejection of claims 1, 93, 94, 96, 97, 99, 107, and 112-121 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in response to Applicant's arguments filed on 10/29/2008.

***Response to Arguments***

***Claim Rejections - 35 USC § 103***

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1, 93, 94, 96, 97, 99, 107, and 110-121 remain under 35 U.S.C. 103(a) as being unpatentable over Tan et al. (Science, 1999, 286: 2352-2355), in view of each Gehrmann et al. (Glia, 1995, 15: 141-151), Gerritse et al. (Proc Natl Acad Sci USA, 1996, 93: 2499-2504), LeBlanc et al. (J Neurochem, 1996, 66: 2300-2310), and Tan et al. (EMBO J, February 2002, 21: 643-652).

Tan et al. teach a method for testing the ability of monoclonal antibodies directed against CD40R to interfere with the CD40L/CD40R signaling pathway in microglia, the method comprising: (i) contacting a first sample of microglial cells with CD40L and measuring the level of the produced TNF-α, (ii) contacting a second sample of activated microglial cells with CD40L in the presence of an anti-CD40R antibody, and measuring the level of the produced TNF-α, and (iii) comparing the level of TNF-α in the first sample with the level of TNF-α in the second sample (claims 1, 93, and 94); the microglia could be derived from transgenic animals overexpressing APP which animals are afflicted with Alzheimer's disease (claims 112, 113, and 116-120) (p. 2353, columns 1 and 2 ; Fig. 4). Tan et al. teach that CD40L binding to the CVD40R on microglia activates these cells and that activated microglia secrete increased amounts of TNF-α; TNF-α level can be used as a marker to determine whether the anti-CD40R antibodies are able to inhibit CD40L/CD40R signaling pathway (p. 2353, columns 1 and 2, p. 2354, column 1). With respect to the limitation of the cells expressing βAPP (claim 1), this is an inherent property of microglia (see LeBlanc et al., Abstract, p. 2302, column 2, p. 2303, column 2). Therefore, Tan et al. teach using cells expressing both CD40 and βAPP (claim 1).

Tan et al. do not teach using the amount of βAPP or fragment thereof as a marker (claim 1). However, the prior art teaches that, similar to TNF-α, βAPP expression is increased in activated microglia. For example, Gehrmann et al., teach that activated microglia in patients affected with multiple sclerosis (MS) exhibit enhanced βAPP levels and that βAPP detection could be a sensitive marker for MS progression (Abstract). Furthermore, Gerritse et al. teach that activated microglia bearing CD40R on their surface are involved in MS progression (Abstract, p. 2499, column 2, second full paragraph, p. 2501, column 2, p. 2502, column 2, p. 2503, columns 1 and 2, p. 2504, column 1). Based on these teachings of CD40L/CD40R signaling pathway leading to Ms and of βAPP level as a marker for MS progression, one of skill in the art would know that activation of microglia by the CD40L/CD40R signaling pathway correlates with increased βAPP expression. It would have been obvious to one of skill in the art, at the time the invention was made, to substitute the TNF-α of Tan et al. with the βAPP of Gehrmann et al. to achieve the predictable result of assessing the ability of anti-CD40R antibodies to inhibit microglial activation in response to CD40L treatment.

With respect to the limitation testing agents being agents capable of binding CD40L (claims 94, 96, and 107), Gerritse et al. teach the advantage of screening for compounds that target CD40L; Gerritse et al. teach that CD40L has advantages over the constitutively and widely expressed CD40R as a target for intervention because its transient expression is restricted to $CD4^+$ T cells, which allows targeting of only those T cells actively participating in the response, without affecting the population of T cells at

large (p. 2504, column 1). Based on these teachings, one of skill in the art would have been motivated to modify the method of Tan et al. by screening for antibodies that interfere with the CD40R/CD40L signaling pathway by binding to CD40L and would have been expected to have a reasonable expectation of success in using such a method because the art teaches the successful use of such methods to identify compounds with the ability of modulating the CD40L/CD40R signaling pathway. It is noted that by doing such, one of skill in the art would have necessarily identified antibodies that would decrease CD40L trimerization (claim 96).

With respect to the limitation of a compound modulating β-amyloid processing (claims 97 and 99) it is noted that the art teaches that microglia process βAPP to yield Aβ (see LeBlanc et al., Abstract; p. 2301, paragraph bridging columns 1 and 2; p. 2303, column 2; p. 2307, column 2, last paragraph). Therefore the antibody used in the method of Tan et al., Gehrmann et al., and Gerritse et al. necessarily modulates β-APP processing. Furthermore, since the art teaches that microglia process βAPP to yield Aβ, it would have been obvious to one of skill in the art to replace βAPP with Aβ in the method of Tan et al., Gehrmann et al., and Gerritse et al. to achieve the predictable result of detecting modulation of the CD40L/CD40R signaling pathway in microglia (claim 121).

Tan et al., Gehrmann et al., and Gerritse et al. do not teach using neuronal cells or the neuroblastoma N2a cells (claims 110 and 111). However, it is noted that the claims are directed to an *in vitro* method of screening for compounds that inhibit CD40L/CD40R signaling pathway by using cells expressing CD40R and βAPP;

therefore, one of skill in the art would have known that the use of any cell expressing CD40 and βAPP would have yielded predictable results, i.e., identification of compounds that inhibit CD40L/CD40R signaling pathway. Applicant did not provide any evidence that the specific use of neuronal or N2a cells would result in unexpected results. Just because Applicant uses another cell type does not render the claims unobvious over the prior art. Moreover, it is noted that the prior the prior art teaches that neuronal cells express CD40R and βAPP (see Tan et al., EMBO J, Abstract, p. 644, columns 1 and 2, p. 645, column 2; LeBlanc et al., Abstract, p. 2303, column 2). One of skill in the art would have known that the substitution of one cell for another cell would render the claimed results and would have known that neuronal or N2a cells could also be successfully employed in the claimed screening assay.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Applicant traversed the instant rejection on the grounds that Gehrmann is a study of the expression of β-APP and its proteolytic fragments in varying neuronal cells during the development of brain lesions associated with Multiple Sclerosis (MS). However, Applicant argues, Gehrmann neither teaches nor suggests that the expression of β-APP in microglial cells is dependent on the activation state of the cells. Although Gehrmann reports that activated microglia in actively demyelinating lesions of MS express β-APP, the reference also indicates that β-APP expression was found on microglia within control tissues: teaching that non-activated microglia also express β-APP (p. 145, first

column, lines 2-7 and Fig. 1). Thus, Gehrmann's teachings demonstrate that β-APP expression may be indicative of active MS lesions, but not that β-APP is a marker of microglial activation. In fact, one of skill in the art would interpret the teachings of Gehrmann to demonstrate that β-APP expression is not linked to the activation state of a microglial cell. Accordingly, Gehrmann provides no suggestion that the expression of β-APP could be substituted for that of TNF-α as a marker for microglial activation or the modulation of CD40L/CD40R signaling as taught by Tan.

With respect to the contention for the further replacement of the expression of β-APP as a marker for microglial activation and/or modulation of CD40L/CD40R signaling, Applicant argues that nowhere does the art demonstrate that the expression of Aβ may substitute for that of β-APP as such a marker. The Examiner references LeBlanc as an alleged teaching that microglia process β-APP to yield Aβ (citing LeBlanc, page 2303, column 2). However, the reference in fact teaches the exact opposite of the Examiner's contention. Although the passage cited by the Examiner indicates that microglia express the full length β-APP protein, it is completely silent as to the protein's further processing in these cells. Where the processing of β-APP to yield Aβ is discussed (LeBlanc, page 2304 column 2, line 13 to page 2305, column 1, line 6), LeBlanc reports that microglia process β-APP to form only p3 (a non-amyloidogenic fragment of β-APP) and not Aβ (see, in particular, LeBlanc, page 2305, column 1, lines 3-6 and FIGS. 4 B and C). Thus, in view of LeBlanc, one of skill in the art would not view the expression of Aβ as a substitute for the expression of β-APP in any assay, generally, much less as a

marker of microglial activation and/or the modulation of the CD40L/CD40R signaling pathway.

Moreover, nowhere in any reference cited by the Examiner is shown that modulation of CD40 activity led to a modulation in APP expression/processing. Only in the present application is it shown that direct modulation of CD40R activity correlates with a modulation of APP processing [0093]. Gerriste is directed to an evaluation of activated microglia in the etiology of MS in a model system, but is completely silent with respect to β-APP expression, thus cannot render the instant claims obvious. Absent the link established in the instant application between CD40 activity and β-APP expression, it is impossible for one of ordinary skill in the art to conclude that β-APP is associated with microglial activation, much less that CD40 activity and β-APP expression are interdependent events as instantly claimed. The conclusion that β-APP expression in microglia cells is directly correlated to modulation of the CD40L/CD40R signaling pathway is beyond the inferences and creative steps a person of ordinary skill in the art could make without direct experimental evidence as provided in the instant application. Therefore, one of ordinary skill in the art would not have a reasonable expectation of success in using β-APP as a marker of CD40L/CD40R signal pathway modulation based on the teaching of Gehrmann and Gerritse, and would not be motivated to replace TNF-α with β-amyloid in the method of Tan.

Applicant's arguments are acknowledged; however, the rejection is maintained for the following reasons:

In response to Applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Therefore, the argument that the Gerritse et al. reference is silent with respect to β-APP expression is not found persuasive. Gerritse et al. do not have to teach each and every claim limitation. If they did, this would have been anticipation and not an obviousness-type rejection.

Applicant argues that, since control microglia express β-APP Gehrmann et al. do not demonstrate that β-APP is a marker of microglial activation. This argument is not found persuasive. There is no requirement for a protein not to be expressed in control microglia in order for the protein to be considered a marker for microglial activation. Tan et al. teach that activated microglia secrete increased amounts of TNF-α as compared to control microglia; Tan et al. use this increased amount of secreted TNF-α as a marker for microglial activation (see the rejection above). Based on these teachings, one of skill in the art would have known that, as long as it is expressed at increased levels over control, a protein can be used to monitor microglia activation. Gehrmann et al. teach that microglial activation in MS results in increased levels of β-APP as compared to control microglia. Gerritse et al. teach that microglial activation in MS is due to the CD40-CD40L interaction. Therefore, the combination of Gehrmann et al. and Gerritse et al. teaches that CD40-CD40L interaction is responsible for increased β-APP levels in activated microglia (see Abstract). Based on the combined teachings of

Tan et al., Gehrmann et al. and Gerritse et al., one of skill in the art would have known that β-APP could be substituted for TNF-α as a marker for microglial activation due to the CD40-CD40L interaction.

Applicant argues that the art does not teach or suggest that the expression of Aβ could substitute for that of β-APP as a marker for microglial activation. Specifically, Applicant argues that LeBlanc et al. do not teach that microglia process β-APP to yield Aβ. These arguments are not found persuasive because. First, it is noted that an obviousness-type rejection is based on the knowledge available in the prior art as a whole. Second, LeBlanc et al. teach that β-APP processing in resting microglia yields Aβ, albeit in very small amounts (Abstract; p. 2301, paragraph bridging columns 1 and 2; p. 2303, column 2; p. 2307, column 2, last paragraph). Furthermore, prior art other than LeBlanc et al., teaches that microglia produce detectable amounts of Aβ from β-APP and that the amount of produced Aβ increases when microglia are activated (see Bitting et al., J. Biol. Chem., 1996, 271: 16084-16089, Abstract, p. 16084, column 2, p. 16085, column 2, p. 16087, column 2, p. 16088, column 1; Fukumoto et al., NeuroReport, 1999, 10: 2965-2969, p. 2967, column 1, p. 2968, Fig. 2 and paragraph bridging columns 1 and 2 p. 2969, column 2; Weigel et al., Acta Neuropathol, 2000, 100: 356-364, Abstract, p. 361, column 2). Based on the teachings in the art as a whole, one of skill in the art would have known that Aβ could be used to monitor microglia activation.

Applicant argues that none of the cited references teaches that the modulation of CD40 activity leads to the modulation of the β-APP processing. This argument is not

found persuasive for the reasons set forth above. The conclusion that β-APP expression in microglia is directly correlated to modulation of the CD40 signaling pathway is not beyond the inferences one of skill in the art could make. Since the art clearly teaches that microglial activation via CD40 leads to increased β-APP production and processing, one of skill in the art would have known that modulating CD40 would necessarily result in modulating β-APP expression and processing. At the time the invention was made, modulating β-APP expression and processing via modulating CD40 pathway would have certainly been within the knowledge and capabilities of one of skill in the art.

Therefore, the rejection is maintained.

***Conclusion***

5. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Bitting et al. (J. Biol. Chem., 1996, 271: 16084-16089), Fukumoto et al. (NeuroReport, 1999, 10: 2965-2969) and Weigel et al. (Acta Neuropathol, 2000, 100: 356-364) were cited in response to Applicant's argument that microglia do not process β-APP to yield Aβ. Specifically, the references teach that microglia do process β-APP to Aβ; moreover, the references teach that activated microglia produce more Aβ than the resting microglia.

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILEANA POPA whose telephone number is (571)272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ileana Popa/
Primary Examiner, Art Unit 1633